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One-pot synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold and base as catalysts†

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Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines *via* intermediate formation of methyl esters is highly efficient and selective when using a catalytic system comprised of supported gold nanoparticles and added base in methanol.

Selective oxidation of alcohols is one of the most important reactions in organic chemistry and finds use in the manufacture of many bulk commodities, high-value fine chemicals, agrochemicals, and pharmaceuticals. Traditionally, oxidations of alcohols are performed with stoichiometric amounts of high-valent inorganic oxidants such as chromate or permanganate, which inevitable leads to the generation of large amounts of metal waste. In the search for a more sustainable chemical production, researchers have put considerable effort into the development of catalytic oxidations using air or molecular dioxygen as the stoichiometric oxidant.[1,2] From the standpoint of green chemistry these aerobic oxidations are attractive, because dioxygen is a cheap and abundant oxidant that produces water as the only by-product.

Since the first fundamental studies by Bond *et al.*,[3] Hutchings,[4] Haruta *et al.*,[5] and Prati and Rossi[6] supported gold nanoparticles have been recognised as surprisingly active and selective catalysts for a number of aerobic oxidations.[7] For instance, supported gold nanoparticles have been used for oxidation of alcohols to aldehydes,[8] carboxylic acids[9] and esters.[10,11] Furthermore, interesting results have been reported for the oxidation of amines and oxidative coupling of alcohols with amines. In particular, supported gold nanoparticles have been used in the synthesis of azo-compounds,[12] imines,[13] secondary amines,[14] and amides.[15]

Although the increasing number of reports on oxidations with nitrogen-containing compounds represents an interesting development, the field still needs further improvement in terms of catalytic efficiency and practical applicability. For instance, under mild reaction conditions the oxidation of alcohols often requires a strongly alkaline solution and in some systems this represents a strong limitation as various side reactions may decrease the selectivity.[2]

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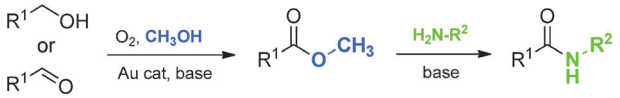


Scheme 1 Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold nanoparticles and base as catalysts.

Here, we show that the combination of supported gold nanoparticles and base forms an efficient and highly selective catalytic system for the one-pot, two-step synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines, see Scheme 1.

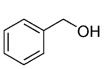
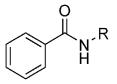
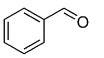
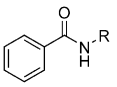
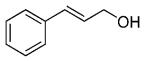
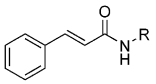
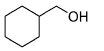
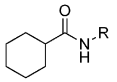
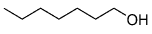
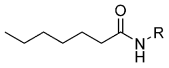
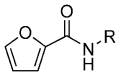
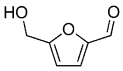
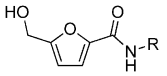
In the first step of the reaction, the gold-catalysed oxidation of the alcohol or aldehyde in methanol yields a methyl ester.[16] In the second step, amine is added and the ester is converted into the desired amide by base-catalysed aminolysis. As the same base is promoting both steps of the reaction, the synthesis can be performed in a convenient one-pot procedure without cumbersome isolation or purification of the intermediate. The employed oxidant is pure dioxygen and the reaction can be performed under mild reaction conditions (25–65 °C, atmospheric pressure).

Initially, we used benzyl alcohol as a model compound to study the gold catalysed oxidative esterification in methanol. The results from these experiments showed that methyl benzoate could be obtained in 92% yield at full conversion after 24 hours employing KOMe as a base and Au/TiO_2 as a heterogeneous catalyst. Under the same reaction conditions, we found that addition of hexylamine to methyl benzoate resulted in the formation of *N*-hexylbenzamide (see ESI†).

The two base-promoted reactions were combined in a novel one-pot reaction procedure and tested for the oxidative coupling of a number of substrates, including different alcohols, aldehydes and amines. All reactions were performed under identical reaction conditions and no optimisation was attempted for the individual substrates.

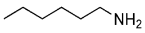
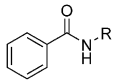
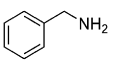
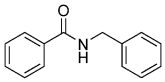
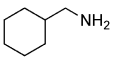
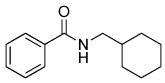
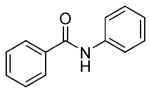
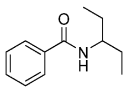
Table 1 compiles the results from the oxidative coupling of different alcohols and aldehydes with *N*-hexylamine to form the corresponding *N*-hexylamides. All examined alcohols, *i.e.* benzyl alcohol, cinnamyl alcohol, and 1-heptanol, were oxidised with high selectivity to form the corresponding methyl ester. While the oxidation of the aromatic alcohols achieved full conversion in 24 hours, 1-heptanol only achieved 34% conversion at room temperature (Table 1, entry 5). Higher yields of aliphatic

Table 1 Yield of ester and amide obtained in the oxidative coupling of alcohols and aldehydes with *N*-hexylamine[a]

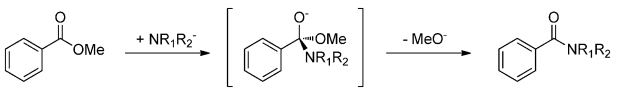
Entry	Alcohol/ aldehyde	Product	Ester yield [%]	Amide yield[b] [%]
1			92	90 (59)
2			93	92 (64)
3			>99	46 (34)
4			74	74 (18)
5			34	34 (25)
6			>99	99 (84)
7			73	73 (73)

[a] R = $(CH_2)_5CH_3$. Reaction conditions: alcohol or aldehyde (5 mmol), methanol (50 mmol), anisole (0.5 mmol), KOMe (1.25 mmol), 1 wt% Au/TiO_2 (197 mg). After 24 hours 25 mmol amine was added and the mixture was heated to 65 °C for additional 96 hours. [b] Number in parenthesis is the yield obtained after 24 hours.

Table 2 Yield of ester and amide obtained in the oxidative coupling of benzyl alcohol with amines[a]

Entry	Amine	Product	Ester yield [%]	Amide yield[b] [%]
1			92	90 (59)
2			92	54 (15)
3			92	38 (16)
4			92	—
5			92	—
6	NH_3	NH_3	92	41[c]

[a] R = $(CH_2)_5CH_3$. Reaction conditions: benzyl alcohol (5 mmol), methanol (50 mmol), anisole (0.5 mmol), KOMe (1.25 mmol), 1 wt% Au/TiO_2 (197 mg). After 24 hours 25 mmol amine was added and the mixture was heated to 65 °C for additional 96 hours. [b] Number in parenthesis is the yield after 24 hours. [c] Isolated yield.



Scheme 2 The reaction pathway from methyl ester to amide *via* an anionic, tetrahedral intermediate, which forms the basis for the computational study.

methyl esters have previously been reported at high temperatures and increased pressure of oxygen.[11] As expected, both aromatic aldehydes, *i.e.* benzaldehyde and furfural, were oxidised to the corresponding methyl esters in high yields (Table 1, entries 2 and 6).

Table 1 also shows that all the investigated methyl esters reacted with *N*-hexylamine to form the corresponding amide in good yields. It is notable that the second step of the reaction occurred with excellent selectivity when using *N*-hexylamine (>99%) independent of the structure of the ester.

Table 2 summarises the results from the oxidative coupling of benzyl alcohol with different amines to form the corresponding amides. The reaction proceeded smoothly when employing benzylamine, while the more sterically demanding amines aniline and pentan-3-amine were unable to react under the applied reaction conditions. Furthermore, the oxidative coupling of benzyl alcohol with ammonia resulted in formation of benzamide.

To investigate the observed structure–reactivity relationship for the aminolysis of methyl benzoate in Table 2 we performed a computational study. The exchange reaction is expected to take place *via* formation of an anionic, tetrahedral intermediate.[17] By determining the relative energies (in solution phase) of the methyl ester, tetrahedral intermediate and amide for the various amines we were aiming to correlate this with the experimental results. The overall process is illustrated in Scheme 2.

We investigated the reaction between methyl benzoate and ammonia, ethylamine, diethylamine, aniline and benzylamine. For the amines larger than NH_3 it was necessary to carry out a thorough conformational search, which was performed using the OPLS-2005 force-field[18] in MacroModel[19] with the built-in GB/SA solvation model (water).[20] The 10 best conformations was then subjected to further optimization using DFT/B3LYP[21] in Jaguar,[22] using the 6-31G** basis set[23] in combination with the PBF continuum solvation model for methanol.[24] To account for the difference in protonation state we used hydroxide, hydronium and water, which were solvated by three additional water molecules.[25] The clusters were embedded in the same PBF solvation model for methanol.

The calculated energetic profiles of the aminolysis for the five different amines are shown in Fig. 1. The three successful examples (NH_3, $EtNH_2$ and $BnNH_2$) all have relatively low energies for both the tetrahedral intermediate and the amide product. In contrast, the amide formed from pentan-3-amine is also thermodynamically favoured by 7 kJ mol^{-1} (similar to ethylamine), but the tetrahedral intermediate is disfavoured by 12 kJ mol^{-1} relative to the one derived from ethylamine. This illustrates that the more sterically demanding pentan-3-amine cannot form the tetrahedral intermediate as the reaction is kinetically controlled.

With aniline the tetrahedral intermediate is similar in energy to the other mono-substituted amines, however, the amide product is almost 40 kJ mol^{-1} higher in energy than the ester.

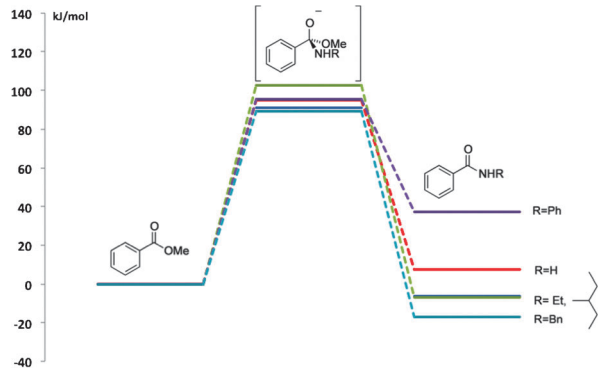


Fig. 1 Calculated energetic profiles for the aminolysis of methyl benzoate using five different amines.

This energy penalty explains why aniline is incapable of converting the ester into the desired amide product.

In conclusion, we have presented a novel approach for the two-step synthesis of amides *via* the corresponding methyl ester and showed that the combination of supported gold nanoparticles and base forms an efficient catalytic system for the reaction. As the same base is promoting both steps of the reaction, the synthesis can be performed in a convenient one-pot procedure without isolation or purification of the intermediate. The employed oxidant is pure molecular oxygen and the reactions can be performed under mild reaction conditions. Furthermore, the reactions can be performed with a number of substrates, which demonstrates the versatility of the method. By employing theoretical DFT calculations we were able to rationalise the differences between successful and unsuccessful amine coupling partners based on a mechanism involving a tetrahedral, anionic intermediate. The good correlation between experiment and theoretical modelling obtained in this study allows us to use DFT calculations in a predictive manner when designing new experiments.

All chemicals and reagents were purchased from a commercial source and used without further purification. The employed catalyst was commercial gold on titanium dioxide (1 wt% Au/TiO_2, supplied by Mintek) with a Brunauer–Emmett–Teller (BET) surface area of 49 $m^2\ g^{-1}$. The size of the gold nanoparticles has previously been determined to be 4–8 nm by means of transmission electron microscopy (TEM).[26]

In a typical experiment, alcohol or aldehyde (5 mmol), anisole (internal standard, 0.5 mmol), base (alkaline metal methoxide, 1.25 mmol) and methanol (50 mmol) were charged to a 20 ml reaction tube and connected to a reaction station providing stirring, heating and O_2 for the oxidation (atmospheric pressure). The system was flushed with O_2 and 197 mg Au/TiO_2 catalyst was added, corresponding to an Au/substrate molar ratio of 1/500. After 24 hours amine (10 or 25 mmol) was added and the reaction mixture was heated to 65 °C for methanol refluxing.

Samples were periodically collected, filtered and analysed by GC-FID and GC-MS using a HP-5 column from Agilent Technologies Inc. The amounts of substrates and reaction products were quantified by correlating to anisole as the internal standard.

The synthesis of benzamide (Table 2, entry 6) was performed in a pressure tube. After oxidising benzyl alcohol in methanol for 24 hours at room temperature under 1 bar of oxygen the tube was cooled in an ice bath and bubbled through with ammonia for 20 min. The tube was then sealed and heated to 65 °C for 24 hours. The reaction mixture was dissolved in water and neutralised to pH 7 by addition of 0.1 M HCl. The product benzamide was recovered by extraction with ethyl acetate which was subsequently removed on a rotary evaporator to give 41% in isolated yield.

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